28. A method for promoting the proliferation of cells, which comprises introducing the polynucleotide of claim 22 together with an expression regulatory sequence into the cells.

B13 29. A method for suppressing the proliferation of cells, which comprises introducing the antibody of claim 25 into the cells.

30. A method for suppressing the proliferation of cells, which comprises introducing the antibody of claim 26 into the cells.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The specification has been carefully reviewed and editorial changes have been effected. All of the changes are minor in nature and therefore do not require extensive discussion. Specifically, the specification headings have been amended in conformance with U.S. practice.

Claims 2, 4, 8 and 9 have been cancelled without prejudice, and claims 1, 3, 5-7 and 10-17 have been amended to put the claims in better form under U.S. practice. Further, new claims 18-30 have been added to further protect the present invention. Support for the claim amendments and new claims is readily apparent from the teachings of the specification and the original claims.

With regard to the objection to the disclosure set forth in item 3 of the Official Action, this objection has been overcome by the insertion of the phrase "*What is claimed is:*" as per the Examiner's request.

With regard to the rejection of claims 1-5 under 35 USC § 101 as set forth in item 4 of the Official Action, this rejection has been overcome by the cancellation of claims 2 and 4 and the amendments to claims 1, 3 and 5. Specifically, claims 1, 3 and 5 have been amended to "*An isolated human protein or gene*" as per the Examiner's suggestion.

With regard to the rejection of claims 8, 9, 14 and 15 under 35 USC § 112, second paragraph as set forth in item 6 of the Official Action, this rejection has been rendered moot by the cancellation of claims 8 and 9, and the amendment of claims 14 and 15 to depend on claims 6 and 7 only.

With regard to the rejection of claims 16 and 17 under 35 USC § 112, second paragraph, as set forth in item 7 of the Official Action, this rejection has been overcome by amending the dependency of claims 16 and 17 to claims 12 and 13, respectively.

With regard to the rejection of claims 2, 4, 6, 7-9 and 12-15 under 35 USC § 112, first paragraph, as set forth in item 9 of the Official Action, this rejection has been overcome by the cancellation of claims 2, 4, 8 and 9, and amendments to claims 6, 7 and 12-15. Specifically, claims 6, 7 and 12-15 have been amended to delete the making or use of additions, deletions or substitutions of one or more amino acids. In other words, the claims are now directed to an isolated human protein or polypeptide comprising the amino acid sequence of SED ID NO: 1 or 2 which the Examiner has indicated to be enabled.

With regard to the rejection of claims 8 and 9 under 35 USC § 112, first paragraph, as set forth in item 10 of the Official Action, this rejection has been rendered moot by the cancellation of claims 8 and 9.

With regard to the rejection of claims 1-17 under 35 USC § 102(a) as being anticipated by Kumagai et al. (Mol. Cell Biol., 1999 Jul; 19(7):5083-95) as set forth in item 12 of the Official Action, this rejection will be overcome by the filing of the verified translation of the certified priority document.

The present application has an effective U.S. filing date of November 1, 1999. The present application also claims priority to Japanese Patent Application No. 1998-311408 filed on October 30, 1998. Applicants wish to note that October 30, 1999 was a Saturday and that the PCT application was filed the following business day which was Monday, November 1, 1999. Therefore, the present application can effectively claim the priority date of October 30, 1998, which is prior to the publication date (i.e. July, 1999) of Kumagai et al.

Thus, since Kumagai et al. has a publication date (i.e. July, 1999) after the priority date (i.e. October 30, 1998) of the present application, this rejection must be withdrawn upon the filing of the verified translation of the certified priority document.

With regard to the rejection of claims 5-7 under 35 USC § 102(e) as being anticipated by Shimkets RA et al. (WO200058473-A2) as set forth in item 13 of the Official Action, this rejection is deemed to be untenable and is thus respectfully traversed.

Applicants wish to note that Shimkets RA et al is not a valid prior art reference since it has a publication date (i.e. October 5, 2000) after the effective U.S. filing date (i.e. November 1,

1999) of the present application. In addition, if the Examiner is citing this international publication of International Patent Application number PCT/US00/08621 which claims priority to various U.S. applications (60/127,607 filed March 31, 1999, 60/127,636 filed April 2, 1999, 60/127,728 filed April 5, 1999, and 09/540,763 filed March 30, 2000), the earliest of which is 60/127,607 filed March 31, 1999, Applicants believe that such a rejection will also be overcome by the filing of the verified translation of the certified priority document since the earliest priority date of March 31, 1999 is still after the priority date (i.e. October 30, 1998) of the present application.

With regard to the rejection of claims 8 and 9 under 35 USC § 102(e) as being anticipated by Penn SG et al. (WO200157278-A2) as set forth in item 14 of the Official Action, this rejection has been rendered moot by the cancellation of the respective claims.

Applicants also wish to note that Penn SG et al. is not a valid prior art reference since it has a publication date (i.e. August 9, 2001) after the effective U.S. filing date (i.e. November 1, 1999) of the present application. In addition, if the Examiner is citing this international publication of International Patent Application No. PCT/US01/00670 which claims priority to various U.S. applications (60/180,312 filed February 4, 2000, 60/207,456 filed May 26, 2000, 09/608,408 filed June 30, 2000, 09/632,366 filed August 3, 2000, 60/234,687 filed September 21, 2000, and 60/236,359 filed September 27, 2000), the earliest of which is 60/180,312 filed February 4, 2000, Applicants believe that such a rejection is still improper since the earliest priority date of February 4, 2000 is still after the effective U.S. filing date (i.e. November 1, 1999) of the present application.

To assist the Examiner in reviewing the priority of Shimkets RA et al. (WO200058473-A2) and Penn SG et al. (WO200157278-A2), Applicants have submitted the first page of each of the respective references.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

Kenichi ARAI et al.

By: _____

Lee Cheng
Registration No. 40,949
Attorney for Applicants

LC/gtg
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
July 15, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The claims have been amended as follows:

1. (Amended) An isolated human [Human H37] protein [having] comprising an amino acid sequence of SEQ ID NO: 1.

3. (Amended) An isolated human [Human H37] protein [having] comprising an amino acid sequence of SEQ ID NO: 2.

5. (Amended) An isolated [A] human gene encoding the human [H37] protein of claim 1 or [2] 3.

6. (Amended) A cDNA of the human gene of claim 5, which [has] comprises a [base] nucleotide sequence of SEQ ID NO: 3 [or a base sequence where one or more base(s) in the base sequence of SEQ ID NO: 3 is/are deleted therefrom, substituted therefor or added thereto].

7. (Amended) A cDNA of the human gene of claim 5, which [has] comprises a [base] nucleotide sequence of SEQ ID NO: 4 [or a base sequence where one or more base(s) in the base sequence of SEQ ID NO: 4 is/are deleted therefrom, substituted therefor or added thereto].

10. (Amended) A recombinant vector [having] comprising the cDNA of claim 6.

11. (Amended) A recombinant vector [having] comprising the cDNA of claim 7.

12. (Amended) An isolated antibody which binds specifically against the human [H37] protein of claim 1 [or 2].

13. (Amended) An isolated antibody which binds specifically against the human [H37] protein of claim 3 [or 4].

14. (Amended) A method for promoting the proliferation of cells, which comprises introducing the cDNA of claim 6 [or the DNA fragment of claim 8] together with an expression[-] regulatory sequence[s] into the cells.

15. (Amended) A method for promoting the proliferation of cells, which comprises introducing the cDNA of claim 7 [or the DNA fragment of claim 9] together with an expression regulatory sequence into the cells.

16. (Amended) A method for suppressing the proliferation of cells, which comprises introducing the antibody of claim [10] 12 into the cells.

17. (Amended) A method for suppressing the proliferation of cells, which comprises introducing the antibody of claim [11] 13 into the cells.

Version with Markings to Show Changes Made

~~DESCRIPTION~~

Human H37 protein and cDNA encoding the Protein

BACKGROUND OF THE INVENTION

1. ~~Technical~~ **Field** of the Invention

This application relates to human H37 protein and to cDNA encoding the protein. More particularly, this application relates to human H37 protein that is an activity-controlling subunit for the protein Cdc7 controlling the replication of human cells; to human gene encoding the protein; to an antibody to the H37 protein; and to a method for controlling the proliferation of human cells using such genetic engineering material and antibody.

2. Description of the Related ~~Background~~ **Art**

Proliferation of cells is initiated when a liquid factor called a growth factor is bound to the receptor on the cell surface and a signal for proliferation is transmitted into the cell. Accordingly, for an artificial induction of proliferation of incubated cells, methods where an excessive amount of a growth factor is added to a cell medium, where a receptor which is not inherently owned by the said cell is expressed on the cell surface and a factor which is specific for the receptor is added to a medium, etc. have been carried out. Further, in suppressing the cell proliferation, methods where competing molecule, antagonist or the like to the receptor protein is added to the medium to suppress the binding of the receptor to the growth factor, etc. have been carried out.

On the other hand, in the case of the cell where a proliferation signal is issued by binding of the receptor to the growth factor, a cycle in which its genomic DNA is replicated, uniformly distributed to daughter cells and then divided is repeated. Such a cycle is called "cell cycle" especially for eukaryotes. The cell

Summary ~~Disclosure~~ of the Invention

This application provides human H37 protein having an amino acid sequence of SEQ ID NO: 1 or NO: 2.

This application also provides human H37 protein having an amino acid sequence where one or more amino acid residue(s) in the amino acid sequence of SEQ ID NO: 1 or NO: 2 is/are deleted therefrom, substituted therefor or added thereto.

This application further provides a human gene encoding the above-mentioned human H37 protein; cDNA of said human gene which has a base sequence of SEQ ID NO: 3 or NO: 4; and DNA fragment comprising a partial sequence of those cDNAs.

This application furthermore provides a recombinant vector having the above-mentioned cDNA and an antibody against the human H37 protein.

This application still further provides a method for promoting the proliferation of cells, which comprises introducing the above-mentioned cDNA or the DNA fragment together with expression regulatory sequence into cell, and a method for suppressing the proliferation of cells, which comprises introducing the above-mentioned antibody into the cell.

Brief Description of the Drawings

Fig. 1 is the result of a western blotting measuring the coimmunoprecipitation of H37 with huCdc7 expressed in mammalian cells. Lanes 1-4, immunoprecipitates; lanes 5-7, whole cell extract. Upper and middle panels ~~pamels~~, immunoprecipitated with anti-huCdc7 antibody No. 1; lower panel, immunoprecipitated with anti- myc antibody. Extracts were prepared from Cos7

cells transfected with huCdc7 in combination with H1 (lanes 2 and 5), H18 (lanes 3 and 6), H37 (lanes 4 and 7) or huCdc7 alone (lane 1). Western blotting was conducted with anti-myc antibody (upper panel) or an anti-huCdc7 antibody No.1 (middle and lower panel).

Fig. 2 is a result of the western blotting measuring antibodies against H37 protein and association of huCdc7 and H37 *in vivo*. Nuclear extracts prepared from Cos7 cells transfected with myc-tagged H37 cDNA were blotted with anti-H37C (lane 1), anti-H37N (lane 2), anti-H37Cpep (lane 3) or anti-myc (lane 4) antibody. The arrow indicates the myc-tagged H37 protein, which carries 63 amino acids derived from 5' non-coding region in addition to the myc-tag. Immunoprecipitations from CEM extracts using either anti-huCdc7Cpep (lanes 5 and 6) or anti-H37Cpep (lanes 7 and 8) were separated on gel electrophoresis and blotted with huCdc7 monoclonal antibody (4A8). The symbols – and + indicates absence and presence, respectively, of each antigen peptide during immunoprecipitation. Lanes 9-13; immunoprecipitates, prepared from nuclear extracts of HeLa cells by anti-huCdc7 No.1 (lane 9), anti-huCdc7 monoclonal antibody 4A8 (lane 10), anti-H37C (lane 11), anti-H37N (lane 12) or anti-H37Cpep (lane 13), were blotted with anti-H37Cpep.

Fig. 3 shows the result of immunoprecipitation by the use of anti-huCdc7 antibody No.1 (lanes 1-5) or anti-myc antibody (lanes 6-10) from the extract of Cos7 cells transfected with myc-tagged H37 alone (lanes 1 and 6), or together with wild-type huCdc7 (lanes 2 and 7), or kinase negative huCdc7 (lanes 3 and 8). Wild-type huCdc7 alone (lanes 4 and 9) and kinase negative huCdc7 alone (lanes 5 and 10) were included as control.

Fig. 4 shows mobility shift of H37 induced by coexpression of wild-type huCdc7. Extracts were prepared from Cos7 cells expressing either wild-type or kinase negative huCdc7 together with myc-tagged H37. Immmunoprecipitates with anti-huCdc7 antibody No. 1 (lanes 1 and 2) or anti-myc antibody (lanes 3 and 4) were blotted with anti-myc antibody (upper) or anti-huCdc7 antibody (lower).

anti-H37Cpep antibody and antigen peptide was microinjected. The pictures show the incorporated BrdU (upper), injected antibody (middle) and cells (lower).

Description of the Preferred Embodiments

~~Best Mode for Carrying Out the Invention~~

The human H37 protein of this invention has the amino acid sequence of SEQ ID NO: 1 and is a protein molecule encoded in the sequence region from 518th to 2541st of cDNA whose base sequence is shown in SEQ ID NO: 3. The H37 protein of this invention also has the amino acid sequence of SEQ ID NO: 2 and is a protein encoded in the sequence region from 518th to 1222nd of cDNA whose base sequence is shown in SEQ ID NO: 4. SEQ ID NO: 3 and NO: 4 are cDNAs derived from mRNA transcribed from the same genomic gene but the cDNA of SEQ ID NO: 4 is in a different splicing form from SEQ ID NO: 3, and there is a deletion from 1199th to 1259th of SEQ ID NO: 3.

Those H37 proteins can be prepared by known methods such as isolation from human organs and cell lines, chemical synthesis of peptide based upon the amino acid sequence provided by this invention, and a recombinant DNA technique using cDNA fragments provided by this invention. For example, in case the H37 protein is prepared by means of a recombinant DNA technique, RNA is prepared from a vector having the cDNA fragment of this invention by an in vitro transcription and then an in vitro translation is carried out using the above as a template whereby an expression in vitro is possible. In addition, when the translational region is recombined to a suitable vector by a known method, it is possible to express the H37 protein encoded in cDNA in a large quantity in Escherichia coli, Bacillus subtilis, yeast, insect cells, animal cells, etc.

When the human H37 protein of this invention is expressed in a microorganism such as E. coli, the translational region of cDNA of this invention is inserted into an expression vector having, for example, promoter, ribosome binding site, cDNA cloning site, terminator, origin replicable in microorganism, etc.

Industrial Applicability

As fully illustrated hereinabove, the present invention provided human H37 protein, a regulatory subunit for Cdc7 that regulate replication of human cells, human gene encoding this protein as well as cDNA thereof, an antibody against H37 protein, and a method for controlling the proliferation of human cells using those genetic engineering materials and antibody. As a result, it provides potentially novel means for preparation of the necessary amount of stem cells or the like to be used for the therapy of various human diseases or for the suppression of proliferation of cancer cells.

PCT [redacted] WORLD INTELLECTUAL PROPERTY OR[redacted]ATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/12, C07K 14/47, 16/18, G01N 33/566, C12Q 1/68, C12N 15/11, 15/62, A01K 67/027, A61K 38/00

A2

(11) International Publication Number: WO 00/58473

(43) International Publication Date: 5 October 2000 (05.10.00)

(21) International Application Number: PCT/US00/08621

(22) International Filing Date: 31 March 2000 (31.03.00)

(30) Priority Data:

60/127,607	31 March 1999 (31.03.99)	US
60/127,636	2 April 1999 (02.04.99)	US
60/127,728	5 April 1999 (05.04.99)	US
09/540,763	30 March 2000 (30.03.00)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	60/127,607 (CIP)
Filed on	31 March 1999 (31.03.99)
US	60/127,636 (CIP)
Filed on	2 April 1999 (02.04.99)
US	60/127,728 (CIP)
Filed on	5 April 1999 (05.04.99)
US	09/540,763 (CIP)
Filed on	30 March 2000 (30.03.00)

(71) Applicant *(for all designated States except US)*: CURAGEN CORPORATION [US/US]; 555 Long Wharf Drive, 11th Floor, New Haven, CT 06511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SHIMKETS, Richard, A. [US/US]; 191 Leete Street, West Haven, CT 06516 (US). LEACH, Martin [GB/US]; 884 School Street, Webster, MA 01570 (US).

(74) Agent: ELRIFI, Ivor, R.; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: NUCLEIC ACIDS INCLUDING OPEN READING FRAMES ENCODING POLYPEPTIDES; "ORFX"

(57) Abstract

The present invention provides open reading frames ORFX, encoding isolated polypeptides, as well as polynucleotides encoding ORFX and antibodies that immunospecifically bind to ORFX or any derivative, variant, mutant, or fragment of the ORFX polypeptides, polynucleotides or antibodies. The invention additionally provides methods in which the ORFX polypeptide, polynucleotide and antibody are used in detection and treatment of a broad range of pathological states, as well as to other uses.

(12) INTERNAT[redacted]L APPLICATION PUBLISHED UNDER TH[redacted]ENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 August 2001 (09.08.2001)

PCT

(10) International Publication Number
WO 01/57278 A2

(51) International Patent Classification[7]: C12Q 1/68, G06F 19/00, C07K 14/47

(21) International Application Number: PCT/US01/00670

(22) International Filing Date: 30 January 2001 (30.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/180,312	4 February 2000 (04.02.2000)	US
60/207,456	26 May 2000 (26.05.2000)	US
09/608,408	30 June 2000 (30.06.2000)	US
09/632,366	3 August 2000 (03.08.2000)	US
60/234,687	21 September 2000 (21.09.2000)	US
60/236,359	27 September 2000 (27.09.2000)	US
0024263.6	4 October 2000 (04.10.2000)	GB

(71) Applicant *(for all designated States except US)*: MOLECULAR DYNAMICS, INC. [—/US]; 928 East Arques Avenue, Sunnyvale, CA 94086 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PENN, Sharron, G. [GB/US]; 617 South Delaware Street, San Mateo, CA 94402 (US). HANZEL, David, K. [US/US]; 988 Loma Verde Avenue, Palo Alto, CA 94303 (US). CHEN, Wensheng [CN/US]; 210 Easy Street #25, Mountain View, CA 94043 (US). RANK, David, R. [US/US]; 117 El Dorado Commons, Fremont, CA 94539 (US).

(74) Agent: RONNING, Royal, N., Jr.; Amersham Pharmacia Biotech, Inc., 800 Centennial Avenue, Piscataway, NJ 08855 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*
— *entirely in electronic form (except for this front page) and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/57278 A2

(54) Title: HUMAN GENOME-DERIVED SINGLE EXON NUCLEIC ACID PROBES USEFUL FOR ANALYSIS OF GENE EXPRESSION IN HUMAN HELA CELLS OR OTHER HUMAN CERVICAL EPITHELIAL CELLS

(57) Abstract: A single exon nucleic acid microarray comprising a plurality of single exon nucleic acid probes for measuring gene expression in a sample derived from human HeLa cells is described. Also described are single exon nucleic acid probes expressed in the HeLa cells and their use in methods for detecting gene expression.